



Decreased Serum Selenium Levels of COVID-19 Patients in Comparison with Healthy Individuals

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Received: 31 March 2021 / Accepted: 16 June 2021

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Abstract

Background Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is the cause of the COVID-19 pandemic and is the cause of increased mortality, especially among elderly patients and those who have severe complications, such as chronic pulmonary obstruction, hypertension, diabetes, and cancer. Nutrition, especially micronutrients, plays an important role in reducing mortality and complications from COVID-19 because micronutrients strengthen our immune system and nutritional status is an important factor that affects the outcome of patients with COVID-19. Among micronutrients, selenium has an important effect on both intrinsic and acquired immunity. Host selenium deficiency affects the viral genome and increases the virulence of viruses. We have investigated the serum selenium levels in COVID-19 patients and healthy control individuals.

Methods A total of 50 patients with COVID-19 infection were included in this study. During hospitalization, 13 patients died (non-survivor group) and 37 patients recovered (survivor group). We assessed the serum selenium levels in 50 COVID-19 patients and 50 healthy individuals by Agilent SpectrAA-240 Z atomic absorption spectrometer.

Results The serum selenium level was significantly lower in COVID-19 patients ($77.8 \pm 13.9 \mu\text{g/L}$) as compared to healthy control individuals ($91.7 \pm 16.7 \mu\text{g/L}$), but there was no significant difference between the survivor and non-survivor groups. Also, there was no significant relationship between serum selenium levels and laboratory findings of COVID-19 patients.

Conclusions These results suggest that decreased serum selenium levels may be a risk factor for the COVID-19 infection, but there was no significant relationship between selenium and severity and mortality of COVID-19 disease.

Keywords COVID-19 · Micronutrient · Selenium · Immune response · Inflammation

Introduction

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is the cause of the COVID-19 pandemic and is the cause of increased mortality, especially among elderly subjects and those who have severe complications, such as chronic pulmonary obstruction, hypertension, diabetes, and cancer [1, 2]. This virus is a single-stranded RNA whose complex metabolism is comparable to other RNA viruses [3, 4]. COVID-19 is a systemic disease with obvious respiratory symptoms. Also, secondary symptoms associated with mortality from the disease include systemic micro thrombosis (a feature of hemorrhagic fever viruses) [5] and heart failure such as myocardial injury (the main feature of Cocksackievirus infection) [6]. The severity of the disease is related to an overreaction of the body's immune system with the release of various cytokines and chemokines "cytokine storm" [7].

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Since no effective treatment for COVID-19 has been identified, all potential therapies, mitigation interventions, and prevention strategies that may reduce the incidence or severity of the infection are critical. Nutrition, especially micronutrients, plays an important role in reducing mortality and complications from COVID-19 because micronutrients strengthen our immune system and nutritional status is an important factor that affects the outcome of patients with COVID-19 [8]. Among micronutrients, selenium has an important effect on both intrinsic and acquired immunity. Selenium enhances the function of CD4+ T cell and B cell and also increases the activity of natural killer (NK) cells [9]. Host selenium deficiency affects the viral genome and increases the virulence of viruses such as coxsackievirus B3 and influenza A [10, 11]. Selenium supplementations have direct antiviral activity in an animal model of the coxsackievirus and influenza. These compounds also have a therapeutic effect on human viral infections such as HIV-1 and hantavirus infections [12]. Like other RNA viruses, SARS-CoV-2 may be affected by selenium status. Activation of nuclear factor kappaB (NF-κB) signaling pathway in various families of viruses increased viral replication and inhibited apoptosis of the virus. This signaling pathway plays an important role in the progression of the COVID-19. Selenium and selenoproteins inhibit NF-κB and decrease viral replication [13]. Blood coagulation disorders that lead to the formation of micro-clots are one of the leading causes of death in patients with COVID-19. Selenium reduces the blood clots forming in the blood vessels [14].

Considering the association of selenium with RNA viruses and mechanisms related to COVID-19, we have investigated the serum selenium levels in COVID-19 patients and healthy control individuals to understand the association between selenium levels and severity and mortality of COVID-19 disease.

Materials and Methods

Study Design

This cross-sectional study, by the ethical principles and the national norms and standards for conducting medical research in Iran, was approved by the Golestan University of medical sciences with an ethics code (IR.GOUMS.REC.1399.297). With the informed consent and before starting treatment of patients, blood samples were taken from all patients admitted to Sayyad Shirazi hospital (academic hospital in Gorgan, Golestan University of medical sciences) who were suspected of having COVID-19. All blood samples were then centrifuged to separate the serum. After centrifugation, the serum samples were stored at -80°C (Sayyad Shirazi hospital) and sent on dry ice to

a Kavosh medical laboratory for analysis (Gorgan, Iran). Patients whose COVID-19 was confirmed by the Real-time PCR were included in this study. Children younger than 18 years of age were excluded. The clinical condition of the COVID-19 patients and the results of white blood cell count, lymphocytes, neutrophils, neutrophil-to-lymphocyte ratio (NLR), platelets, lactate dehydrogenase (LDH), hospitalization time, and age were extracted from electronic medical records. The healthy control group consisted of 50 individuals who were matched with the patient group in terms of age and sex.

Selenium Analysis

Concentrations of selenium have been analyzed by Agilent SpectrAA-240 Z atomic absorption spectrometer equipped with Zeeman background correction and fitted with a PSD-120 sampler by graphite furnace and graphite tubes with integrated L'vov platform. The measured wavelength of selenium was 196.0 nm. The serum samples were prepared according to the method described by Jacobson and Lockitch [15]. Briefly, the samples were diluted with reducing agent including ascorbic acid, Triton X-100, and Antifoam B emulsion, and then, palladium chloride as a matrix modifier was added.

Statistical Analysis

Statistical analysis in this study was performed using SPSS16. Shapiro-Wilk test was used to investigate the normal distribution of data. Data on age, hospitalization time, and laboratory findings were expressed as medians and the interquartile range (IQR), whereas the value of serum selenium level was expressed as means and the respective standard deviations (Mean ± SD). *T*-test was used to compare the two groups. Correlations assessment was performed by Spearman's correlation test. *p*-values < 0.05 were considered significant.

Results

Patient Characteristics

A total of 50 patients with COVID-19 infection were included in this study. During hospitalization, 13 patients died (non-survivor group) and 37 patients recovered (survivor group). The median time to recovery and death was 6 and 12 days, respectively. The median age of the 50 COVID-19 patients was 56.0 years (interquartile range 43–70 years), and most patients were male. The differences in age, lymphocyte count, platelet count, neutrophil-to-lymphocyte ratio, and lactate dehydrogenase on admission between the

survivor and non-survivor group were statistically significant ($p < .05$) (Table 1).

Selenium Status Analysis

The mean serum selenium level in COVID-19 patients was $77.8 \pm 13.9 \mu\text{g/L}$, while it was $91.7 \pm 16.7 \mu\text{g/L}$ in the healthy control group. The difference in selenium level between the two groups was statistically significant ($p < .05$) (Table 2). In COVID-19 patients, serum selenium levels were higher in males than in females, while in the healthy control group, it was higher in women than in men. In both groups, this difference was not significant ($p > .05$).

In the comparison between the survivor and non-survivor groups, the mean serum selenium level in the survivor group was $77.9 \pm 14.3 \mu\text{g/L}$, which was not significantly different from the mean serum selenium level in the non-survivor group, which was $77.2 \pm 12.3 \mu\text{g/L}$ ($p > .05$).

No statistically significant correlation was found between age and serum selenium level in COVID-19 patients and the healthy control group ($r = 0.268$; $p > .05$). There was no significant relationship between selenium and prognostic factors of severe COVID-19 disease such as lymphopenia ($r = -0.298$; $p > .05$), thrombocytopenia ($r = -0.016$; $p > .05$), leukocytosis ($r = -0.019$; $p > .05$), neutrophil-to-lymphocyte

Table 2 Comparison of selenium levels between the COVID-19 patients and the healthy control group

	COVID-19 patients	Healthy control group	<i>p</i> value
Serum selenium [$\mu\text{g/L}$], mean $\pm$ SD			
Total	77.8 ± 13.9	91.7 ± 16.7	0.001
Female	77.8 ± 16.7	95.8 ± 18.8	
Male	77.8 ± 12	88.4 ± 14.5	

SD standard deviation. *Significant group difference at $p < 0.05$. Data were expressed as mean $\pm$ SD

ratio ($r = 0.026$; $p > .05$), lactate dehydrogenase ($r = -0.274$; $p > .05$), and hospitalization time ($r = 0.152$; $p > .05$).

Discussion

In this study, our results showed that serum selenium levels in COVID-19 patients were lower than in the healthy control group. Our results suggested that decreased serum selenium levels may be a risk factor for the COVID-19 infection, and these results were consistent with other studies. A study in Germany reported that the serum level of selenium was meaningfully lower in the surviving

Table 1 Clinical characteristics of the COVID-19 patients

	Survivor ($n = 37$)	Non-survivor ($n = 13$)	<i>p</i> value
Age (years), median with (IQR)	49 (42–66)	72 (65–77)	$< 0.001^*$
Sex, no. (%)			
Female	16 (43.2%)	3 (22.2%)	$< 0.001^*$
Male	21 (56.8%)	10 (77.8%)	
Hospitalization time			
Median with (IQR)	6 (4–8)	12 (7–21)	0.071
Serum selenium [$\mu\text{g/L}$], mean $\pm$ SD	$77.9 \pm 14.3 \mu\text{g/L}$	$77.2 \pm 12.3 \mu\text{g/L}$	$p > .05$
Laboratory findings			
Median with (IQR)			
No. (%)			
White blood cell count, $\times 10^9/\text{L}$	6.1 (4.9–7.9)	6.2 (3.9–12.2)	0.851
< 4	5 (13.5%)	3 (23.1%)	
4–10	28 (75.6%)	5 (38.4%)	
> 10	4 (10.9%)	5 (38.5%)	
Lymphocyte count, $\times 10^9/\text{L}$	1.2 (1–1.6)	0.9 (0.6–1.3)	0.037
< 0.8	3 (8.1%)	5 (38.5%)	
Neutrophil count, $\times 10^9/\text{L}$	3.7 (2.6–5.4)	4.7 (2.8–9.8)	0.162
Neutrophil-to-lymphocyte ratio	2.2 (1.9–4.2)	6.3 (4–8.2)	$< 0.001^*$
Platelet count, $\times 10^9/\text{L}$	194 (141–263)	134 (105–210)	0.014*
4 (10.8%)		3 (23.1%)	
Lactate dehydrogenase, U/L	631 (430–797)	993 (746–1379)	
> 245	36 (97%)	12 (92.3%)	0.015*

IQR interquartile range, no. number, SD standard deviation. *Significant group difference at $p < 0.05$. Data were expressed as median with IQR, mean $\pm$ SD, or numbers and percentages

COVID-19 patients compared to healthy controls [16]. Another study in China also found that the cure rate of COVID-19 disease was significantly correlated with selenium status [17]. A study conducted in South Korea showed that selenium deficiency in COVID-19 patients may reduce the immune response and cause disease progression [18]. Also, a study in the south Indian population reported that serum selenium levels in COVID-19 patients were lower than in the healthy control group [19]. However, the mean serum selenium level of COVID-19 patients in Golestan province was higher than in other studies. According to the sources of selenium in the soil and water of each region, selenium status is different in various parts of the world. Studies in Golestan province showed that selenium levels were high in the soil, grains, loess, sediments, nail, and serum samples [20–22]. These results may explain the difference in selenium levels in our study with other studies. In this study, there was no significant difference between serum selenium levels in the survivor and non-survivor groups. These results were in contrast to the results of the study in Germany [16]. In this study, the mortality of COVID-19 patients was higher in men and elderly patients. Studies show that the death of COVID-19 patients is associated with factors such as obesity, diabetes, male sex, age, asthma, and other chronic diseases [23]. The association between sex and disease severity may be due to differences in the immune response to viral infection in male and female patients. For instance, T cell response in female patients is stronger than in male patients. Furthermore, pro-inflammatory factors such as IL-8 and IL-18 are higher in male patients [24]. The association between older age and COVID-19 mortality can be due to age-related dysfunction in T lymphocyte and B lymphocyte and increased type 2 cytokines production, which leads to impaired control of virus replication and ultimately leads to poor outcome [25]. Selenium is an essential trace element that exerts its main function on the health of the body through selenocysteine in the structure of selenoproteins [26, 27]. Adequate levels of selenium are essential for central nervous system function, male reproduction, endocrine system, muscle function, cardiovascular system, and immune system [28]. Viral infection in host cells increases reactive oxygen species (ROS) formation. Increased ROS lead to oxidative stress and increased oxidative stress enhance viral genome mutations and increase virulent strains. Glutathione peroxidase 1 (GPX1) is a cytosolic selenoprotein with antioxidant and antiviral properties [29]. A study in mice lacking the Gpx1 gene showed that infecting mice with the benign type of RNA coxsackievirus B3 caused mutations in the viral genome, augmented virulence, and myocarditis, this condition was not observed in wild-type mice [30]. Also, both wild-type selenium-deficient mice [30] and Gpx1^{−/−} mice [31]

infected with influenza A show an increased inflammatory response and severe lung damage. These results propose that Gpx1, as an enzyme most affected by selenium status, may play a protective role in respiratory viral infections. The factors associated with the severity of COVID-19 disease include exhaustion of NK cells and cytotoxic T lymphocytes (CTL) [32]. Studies show that selenium supplementation increases the proliferation of T cells and NK cells and the function of the innate immune system [33, 34]. IFN- γ and TNF- α secreted by CTL have an antiviral activity to the influenza virus [35]. In infected mice with RNA influenza virus, selenium supplementation increases levels of IFN- γ and TNF- α in plasma [36]. Inflammatory factors IL-1 β and IL-6 are the causes of pneumonia. In patients with severe COVID-19 disease, the IL-6 level is high and a high level of IL-6 is associated with mortality of disease [37, 38]. Studies show that in the elderly, greater levels of IL-6 are associated with selenium deficiency [39]. In conditions of selenium deficiency in cell culture, lung epithelial cells infected with influenza type A increase production of IL-6 [40]. Selenium supplementation inhibits the induction of IL-6 in mice under oxidative stress [41]. Furthermore, the IL-6 response is reduced by selenium [10, 42]. Selenium in patients with acute respiratory distress syndrome (ARDS) modulates inflammatory responses and improves the antioxidant capacity of the lungs [43]. Increased coagulation activity may be related to increased mortality in COVID-19 patients [44]. Also, studies have reported that the occurrence of thrombotic complications is high in patients with COVID-19 [45]. Selenium controls the arachidonic acid pathway by regulating the synthesis of thromboxane A2 and pro-inflammatory products of lipoxygenase [46]. Selenium deficiency by increasing the ratio of thromboxane A2 to prostacyclin may be associated with vasoconstriction and blood coagulation [47]. The prognostic factors in COVID-19 patients are lymphopenia, thrombocytopenia, leukocytosis, neutrophil-to-lymphocyte ratio, and LDH [48, 49]. Studies show that the plasma selenium level is inversely related to clinical markers of infection and inflammation, such as leucocyte count, serum CRP, and serum IL-6 [50]. In this study, there was no significant relationship between selenium and prognostic factors such as lymphopenia, thrombocytopenia, leukocytosis, neutrophil-to-lymphocyte ratio, and LDH in COVID-19 patients.

In summary, this study investigated the selenium levels in COVID-19 patients. The results showed that although serum selenium levels in COVID-19 patients were lower than in the healthy control group, there was no significant relationship between selenium and severity and mortality of COVID-19 disease. Further research is needed on the association of selenium with pathogenic factors in a larger population of COVID-19 patients.

Acknowledgements The authors would like to thank the Golestan University of Medical Sciences, Gorgan, Iran, for financial supporting and Kavosh medical laboratory for analysis of serum selenium.

Author Contribution Ommolbanin Younesian wrote the paper. Behnaz Khodabakhshi contributed data or analysis tools. Nafiseh Abdolahi contributed data or analysis tools. Alireza Norouzi conceived and designed the analysis. Nasser Behnampour performed the analysis. Sara Hosseinzadeh collected the data. Seyedeh Somayeh Hosseini Alarzi collected the data. Hamidreza Joshaghani wrote the paper and conceived and designed the analysis.

Funding This research is supported by the Laboratory Sciences Research Center, Golestan University of Medical Sciences, Gorgan, Iran.

Data Availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics Approval This study was approved by the Ethics Committee of Golestan University of Medical Sciences with an ethics code (IR.GOUMS.REC.1399.297). All procedures performed were in agreement with the principles of the Declaration of Helsinki (1964) and later amendments.

Consent to Participate Informed consent was obtained from all individual participants included in the study.

Consent for Publication Not applicable.

Competing Interests The authors declare no competing interests.

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- Acknowledgements** The authors would like to thank the Golestan University of Medical Sciences, Gorgan, Iran, for financial supporting and Kavosh medical laboratory for analysis of serum selenium.
- Author Contribution** Ommolbanin Younesian wrote the paper. Behnaz Khodabakhshi contributed data or analysis tools. Nafiseh Abdolahi contributed data or analysis tools. Alireza Norouzi conceived and designed the analysis. Nasser Behnampour performed the analysis. Sara Hosseinzadeh collected the data. Seyedeh Somayeh Hosseini Alarzi collected the data. Hamidreza Joshaghani wrote the paper and conceived and designed the analysis.
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- Consent for Publication** Not applicable.
- Competing Interests** The authors declare no competing interests.
- References**
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